C2

16. (Twice Amended) The pair of vectors of claim 12 wherein the component of an LCR is a component of the β-globin LCR selected from the group consisting of HS3 and HS4, and combinations thereof.

REMARKS

This paper is filed in response to the Final Rejection dated October 4, 2000. A petition for a three-month extension of time, and the appropriate fee, accompany this response.

Claims 1-21, 23, and 25 were pending. All pending claims were rejected in the Final Rejection.

Claims 5 and 16 have been amended herein. In view of the foregoing amendments and arguments that follow, Applicants respectfully request withdrawal of all rejections upon reconsideration.

Preliminarily, Applicants thank the Examiner for the helpful interview conducted on December 12, 2000. Pursuant to that interview, Applicants enclose herewith the Declaration of Dr. Crombie ("the Declaration"). In the Declaration, Dr. Crombie discusses data obtained with the CD2 LCR, and data showing the tissue specificity of HS2 and a combination of HS2, HS3, and HS4.

Additionally, Applicants submit herewith a PTO-1449 form citing Aleshkov et al., *Molecular Biology*, 28(3):411-414 (1994) ("Aleshkov") discussed during the interview. As clarified therein, the reference to "LCRs" in Aleshkov is to something different than a Locus Control Region as contemplated by the present invention. As defined in Aleshkov, LCR refers to a long control region at the 5' terminus of the Bovine Papilloma Virus 1 early region (see page 411, column1, n. 1). There is no mention or suggestion of the tissue specificity attributed to Locus Control Region. See U.S. Patent No. 5,736,359 issued to Grosveld and Kioussis, copy attached. Locus Control Regions are referred to therein alternatively as dominant activator sequences or dominant control regions Further, as discussed in the paragraph bridging columns 1 and 2 on page 412 of Aleshkov, most of the vector molecules were not maintained as episomes, but were actually integrated into the genome.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 5, 14, and 16 were again rejected in the Final Rejection for the reasons of record advanced in the Office Action mailed 3/15/00, i.e., as allegedly indefinite in view of the recitation "consisting essentially of." Claims 5 and 16 are amended herein. Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-3, 5-14, and 16-21 were again rejected as allegedly unpatentable over Yates et al., Sadelain et al., Greaves et al., Grosveld et al., Ustav et al., and Svensson et al.

During the interview discussed above, the Examiner indicated that this rejection would be dropped based upon the argument that there is no expectation of success for using the LCR in the context of an episome.

Briefly, as discussed during the interview, and as set forth in the Declaration, the dogma at the time the present application was filed was that LCRs worked in integrating vectors and that is how tissue specificity was conferred. It was not expected that tissue specificity would be conferred on an episomal vector.

The references relied upon by the Examiner did not show otherwise. Sadelain et al. report that when the LCR is minimized, i.e., reduce to three of the core sequences, position-independent expression becomes copy number dependent. Sadelain et al. used various sense and antisense combinations of the core sequences HS2, HS3, and HS4. Contrastingly, Applicants achieved the high levels of expression with only these three core sequences. Further, Sadelain et al. conclude that "it is important to carefully reevaluate the characteristics of larger LCR-containing sequences in the context of **single**-copy insertions " (emphasis supplied). Sadelain et al. continues, noting the importance of obtaining position-independent expression with **single** copy insertions for effective gene therapy. Sadelain et al. does not disclose or suggest Applicants invention. (See paragraphs 7-9 of the attached Declaration.)

Svennson et al. is similarly unavailing. Svennson et al. do **not** describe a self-replicating episomal vector. (See paragraph 10 of the attached Declaration.)

Claim 23 was again rejected in the Final Rejection as allegedly unpatentable over the references cited above as applied to claims 1-3, 5-14, and 16-21, further in view of Chapman et al.

Applicants respectfully traverse this rejection.

The deficiencies of the references cited for claims 1-3, 5-14, and 16-21 are discussed above, discussion incorporated herein. Chapman et al. does not overcome these deficiencies. Chapman et al. is relied upon for the transfection of cultured cells. Chapman et al., however, does not disclose or suggest the use of an LCR in an episomal vector. Applicants request that this rejection be withdrawn.

Claim 25 was again rejected in the Final Rejection as allegedly unpatentable over the references cited for claim 23. Applicants respectfully traverse this rejection.

The deficiencies of the references cited for claims 1-3, 5-14, and 16-21 are discussed above, discussion incorporated herein. Chapman et al. does not overcome these deficiencies. Chapman et al. is relied upon for disclosing the effect of intron A from human cytomegalovirus immediate early gene on heterologous expression in mammalian cells. Chapman et al., however, does not even suggest testing candidate regulatory elements, much less LCRs. The Examiner made a giant leap from Chapman et al. to finding testing candidate LCR sequences as claimed obvious. Applicants respectfully request that this rejection be withdrawn.

For the foregoing reasons, the Applicants submit that the present description and claims meet all the requirements for patentability. The Examiner is respectfully requested to allow all the present claims.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version With Markings To Show Changes Made."

Respectfully submitted

Date: April 4, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 5 and 16 were amended as follows:

5. (Twice Amended) The self-replicating episomal DNA expression vector of claim 2 wherein the component of an LCR is a component of the β-globin LCR selected from the group consisting of HS3 and HS4, and [or] combinations thereof.

16. (Twice Amended) The pair of vectors of claim 12 wherein the component of an LCR is a component of the β-globin LCR selected from the group consisting of HS3 and HS4, and [or] combinations thereof.